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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/925,970	08/10/2001	Ashok Amin	AMIN4A	4363

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BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, DC 20001

EXAMINER	
WORTMAN, DONNA C 11	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 03/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/925,970	AMIN ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/27/03, 3/5/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 27, 2003, has been entered.

Claims 3 and 4 were amended and claims 7-13 were added in Paper No. 9, filed February 27, 2003. Claims 14 -18 were added in Paper No. 10, filed March 5, 2003.

Accordingly, claims 1-18 are pending and under examination.

The amendment filed February 27, 2003, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment to the specification at page 1, paragraph [0005], is deemed to be new matter because it substitutes "TNFalpha" for "TNFRalpha" at line 2. It is apparent that substituting a cytokine, TNF alpha, for its receptor, TNFR alpha, changes the meaning of the specification as originally filed and constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 6, 13, 17, and 18 are objected to because of the following informalities:

In claims 6, 13, and 18, "infliximab" is misspelled.

In claim 13, at the beginning of line 2, "whiten" should read "wherein."

In claim 13, line 3, "humanize" should read "humanized."

Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims fail to correspond in scope with that which applicants regard as the invention can be found in Paper No. 9 filed February 27, 2003. In that paper, applicant has stated (1) that claims 3 and 4 have been amended to make it clear that the compound that neutralizes the effect of secreted TNF alpha is a compound that inhibits the production of p75:FC and this statement indicates that the invention is different from what is defined in the claims because claims 3 and 4 do not recite inhibiting the production of p75:FC.

Claims 3, 4, 10, 15, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 4, 10, 15, and 16 confusingly recite either "inhibiting p75:FC" or "inhibits p75:FC" or "inhibits p75:FC inhibitor." Since claims that depend from claims 3, 4, 10, 15, and 16 recite that the antecedent compound is etanercept, and since etanercept, by Applicant's own definition, which is consistent with the terminology recognized in the art, is a fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1, i.e., is represented by p75:Fc, the claims are indefinite; it

is not understood how etanercept can both inhibit "p75:FC" (or p75:Fc) and be represented by the terminology p75:FC. Applicant is requested to use claim terminology that is both consistent with the definitions supplied by the specification and recognized in the art in order to prevent confusion. If Applicant believes that "p75:FC" does not refer to the structure of a fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1, Applicant is requested to clarify what is intended by that terminology and to point to the portion of the specification that provides and supports another definition.

In addressing the rejection of claims 3 and 4 previously made under 35 USC 112, second paragraph, Applicant has argued "the present inventors have discovered that etanercept and infliximab inhibit p75:FC, and therefore it is not unreasonable to claim a new function for a known compound." This argument is not understood, since, as discussed above, it is believed that "p75:FC" describes the structure of etanercept; it remains unclear what Applicant intends to claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, essentially for reasons of record in rejecting claims 1-6

previously. The claims are drawn to a method for treating any type of hepatitis (claims 1, 3-5, 7) or a method for treating various types of viral hepatitis (claims 2, 9, 14) by administering a compound that neutralizes the effect of secreted TNF alpha (claims 1, 2, 8, 10, 15) which may be either "a p75:FC inhibitor" (claims 3, 4, 11, 15) or a humanized monoclonal antibody (claims 5, 6, 12, 13, 17, 18). The specification teaches the administration of etanercept to a single patient with rheumatoid arthritis and hepatitis C, after which the patient showed an improvement in arthritis symptoms, transaminase levels and viral RNA levels. It is apparent that one of skill in the art would not be able to extrapolate from the results from administering a single compound, etanercept, to a single patient with rheumatoid arthritis and hepatitis C, to obtain a method of treating any type of hepatitis, viral or nonviral, by administering any compound that can be interpreted as neutralizing the effect of secreted TNF alpha as is claimed. Even if the claims were to be limited to treating hepatitis C by administration of etanercept, the specification would not teach one of skill in the art how to practice the invention as claimed, since a result observed in a single patient is not seen to enable a treatment method. The state of the art at or near the time the invention was made is properly considered in evaluating enablement. Campbell et al. (European Journal of Gastroenterology and Hepatology 13(2):191-192, 2001), of record (not prior art), disclose treatment of a patient with Crohn's disease, who also had chronic hepatitis C, with infliximab. Campbell et al. report no change in the raised level of the liver enzyme alanine aminotransferase and, despite the fact that the PCR for HCV was reported to be negative at 16 weeks follow-up, Campbell et al. do not suggest that infliximab is a

treatment for hepatitis C, but rather interpret this result observed in a single patient differently: "... it would appear that in this particular case infliximab therapy was not detrimental to ongoing HCV infection" (page 192). Campbell provides evidence that a single case report does not provide those of skill in the art with sufficient teaching to practice a method of treatment, since the lack of a bad result in a single case cannot be extrapolated to a reasonable expectation for success in obtaining a generally beneficial result as is required in order to enable a treatment method.

Peterson et al. (Arthritis Rheum. 44(9):Suppl., November 2001, page S78), of record, in summarizing the treatment of nine patients with rheumatoid arthritis and chronic hepatitis C with either etanercept or infliximab, report that "LFT and HCV viral load measurements are usually not affected by short-term use of TNF-α antagonists."

Tilg et al. (Hepatology Vol. 34, No. 4, Pt. 2, October 2001, p. 696A), of record, discloses treatment of two HCV-positive patients with severe alcoholic hepatitis with infliximab. One patient remained HCV RNA negative and HCV antibody positive after treatment, and the second patient showed decreased liver inflammation, interpreted by the authors as an improvement in alcoholic hepatitis, but also showed an increase in HCV viral replication. The authors concluded that "The effect of TNF-neutralization in HCV positive liver disease warrants further study."

Hayat et al. (Clinical Immunology Vol. 103, No. 3, Part 2, Supp., June 2002, p. S80), of record, discloses the effect of infliximab therapy for rheumatoid arthritis in a patient with chronic hepatitis C. After 6 weeks of infliximab the patient was started on interferon and ribavirin. HCV viral load increased 1.69×10^7 copies/ml 1 week post

treatment and then returned to pretreatment baseline 2.96 x 10^6 copies/ml. There was no change in the level of pro- and anti-inflammatory cytokines and liver function tests with therapy.

Biancone et al. (Gastroenterology Vol. 122, No. 2, pp. 593-594), of record, discloses the use of immunomodulatory drugs in Crohn's disease patients with hepatitis B or C virus Infection. See, e.g., Table 1, Pt. 8: treatment with infliximab resulted in no clinical effect on liver disease.

Those of skill in the art, who have done what Applicant has disclosed and claimed, have not achieved a reasonable expectation for success in obtaining a generally beneficial result as is required in order to enable a treatment method.

Applicant has argued that the presence of only one working example should not be the sole reason for rejecting claims; that a disclosure of every operable species is not required; that Applicant has demonstrated that compounds that neutralize the activity of secreted TNF, such as a ligand binding protein of the human p75 TNF receptor linked to human IgG1 Fc, or a humanized monoclonal antibody that neutralizes the activity of TNF, can be used "to reverse evidence of hepatic inflammation associated with active hepatitis and to reduce the viral load by 80%"; that the specification at paragraph [0019] describes use of "TNF neutralizing compounds in a plurality of patients" which is evidence of successful treatment.

These arguments have been considered but not found persuasive. It is appreciated that the presence of only one working example should not be the sole reason for rejecting claims and that a disclosure of every operable species is not

required; however, the presence and the number of working examples can reasonably be taken into consideration in determining enablement. A close reading of paragraph [0019] indicates that a plurality of patients with rheumatoid arthritis were treated but does not make clear that a plurality of the treated patients also had hepatitis, or that a plurality of patients with hepatitis were treated and benefited from treatment, and does not make clear whether the reduction of viral load by 80% relied upon above was a result achieved in a "plurality" of patients or whether it was the reduction in viral load found in the single patient described in the example. Further, the references cited above that report results for a plurality of hepatitis patients treated with etanercept or infliximab do not support a reasonable expectation for success in achieving therapeutic benefit from the treatment, including but not limited to reduction in viral load.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 7, 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by The Merck Manual of Diagnosis and Therapy (Beers et al., Eds., Seventeenth Edition, published by Merck Research Laboratories, 1999) pages 384-386, of record, essentially for reasons of record in rejecting claims 1 and 2 previously. The Merck Manual discloses treatment of autoimmune hepatitis with corticosteroids and treatment of hepatitis B and hepatitis C with interferon alpha, and discloses that both treatments result in reduction of inflammation. Interferon alpha reduces viral levels in patients with

hepatitis C. Since the cited claims do not require direct interaction with TNF or TNF receptor, the hepatitis treatments disclosed by the Merck Manual are deemed to anticipate the claims.

Applicant has argued that the Merck Manual does not mention neutralizing the effects of TNF alpha; that the reference teaches that results of using interferon to treat hepatitis are reported to be "relatively disappointing" and therefore it teaches away from using interferon.

These argument have been considered but not found persuasive. Inflammation is an effect of secreted TNF alpha and Applicant has previously stated on the record that "the mechanisms by which this is accomplished is immaterial (*sic*; Paper No. 6 submitted 6/25/02, page 6). The rejection was made under 35 USC 102(b), not under 35 USC 103, and since it actually discloses treatment of hepatitis with interferon, it cannot be interpreted as "teaching away."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw
March 18, 2003